

Chemical structure of the hybrid molecule, Endomorphin II-Substance P7-11. The structure shows the N-terminus of Endomorphin II (a benzylmorphine derivative) linked via a peptide bond to the C-terminus of Substance P7-11 (a heptapeptide). The Endomorphin II portion includes a morphine ring system with a 3-hydroxyphenyl group and a protonated amine. The Substance P7-11 portion includes a heptapeptide chain ending in an amide group. The two molecules are connected by a single peptide bond between the C-terminal amino acid of Endomorphin II and the N-terminal amino acid of Substance P7-11.

FIG. 1

Chemical structure of the hybrid peptide [Pro⁹]Substance P7-11-Endomorphin II. The structure shows a linear sequence of amino acids with two bicyclic endomorphin-like motifs. The first motif is linked to a 4-hydroxyphenyl group, and the second is linked to a 4-phenylphenyl group. The C-terminus is a 4-methylthioethylamide. Below the structure, two arrows indicate the regions corresponding to Endomorphin II (residues 1-10) and [Pro⁹]Substance P7-11 (residues 7-11).

FIG. 2.

Binding of ESP7 to the Mu Receptor

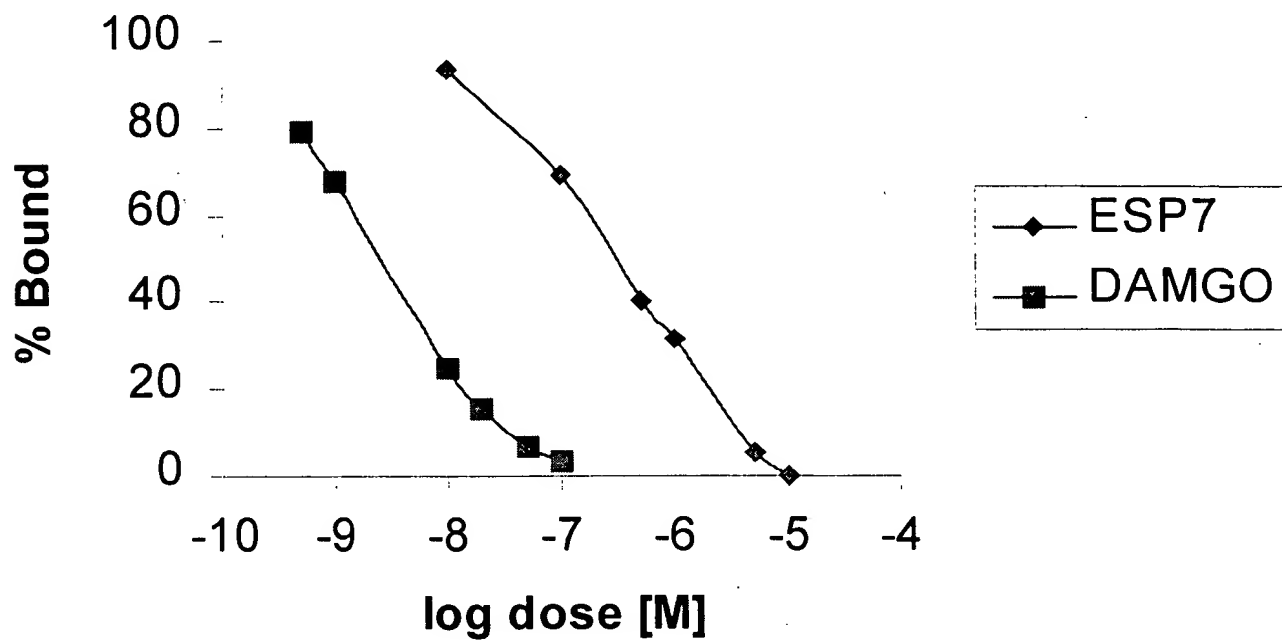


Figure 3

6652307 26582160

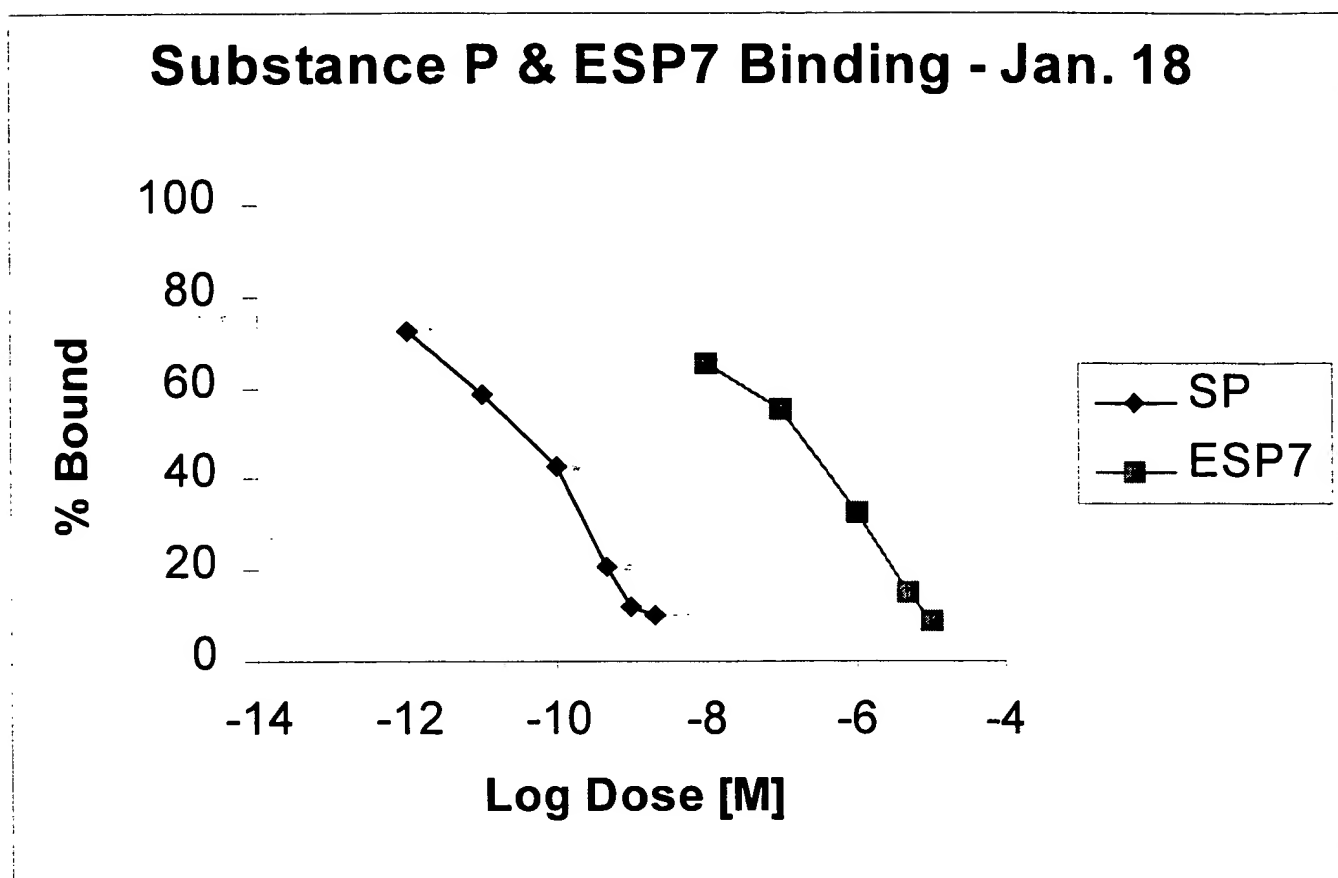


Figure 4

Intrathecal Administration

1.0 ug ESP7+2CD (n=5)

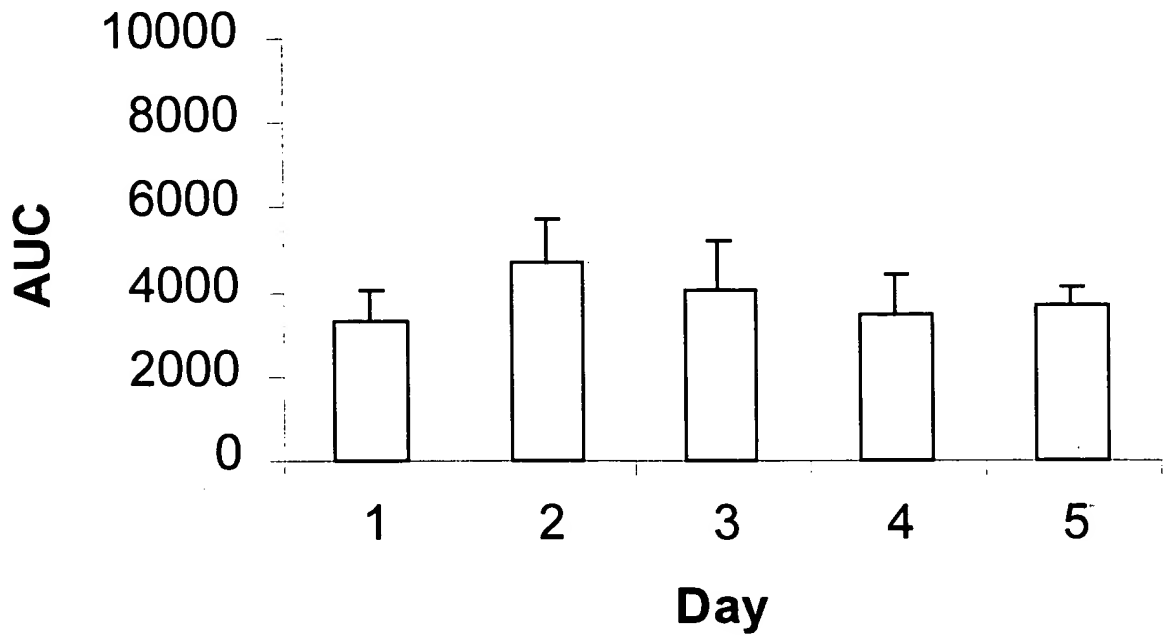


Figure 5.

0.2 ug ESP7+2CD (n=8)

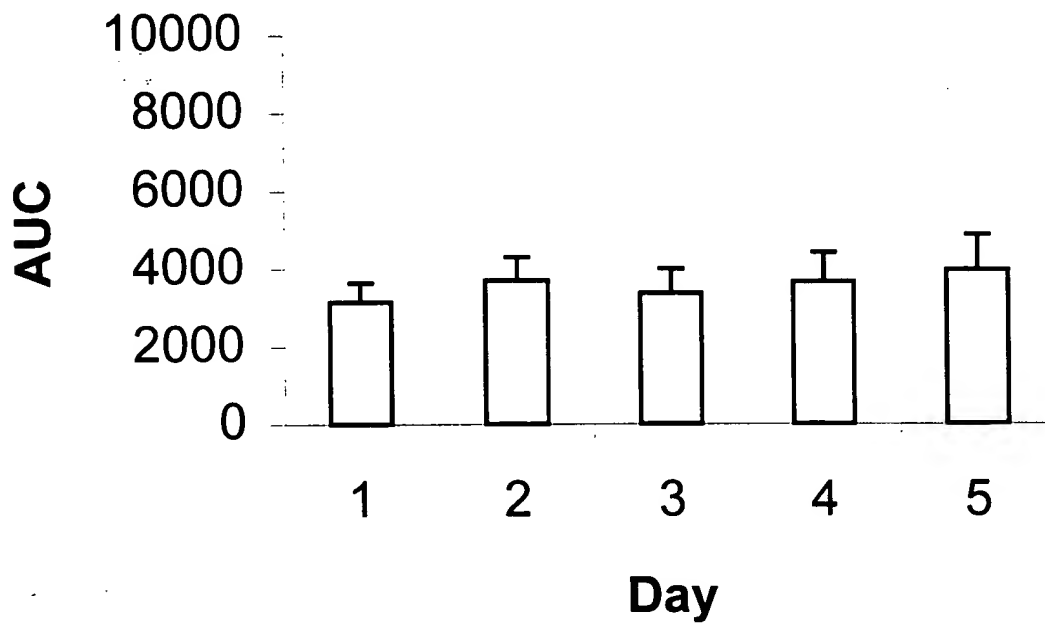


Figure 6

0.05 ug ESP7+2CD (n=6)

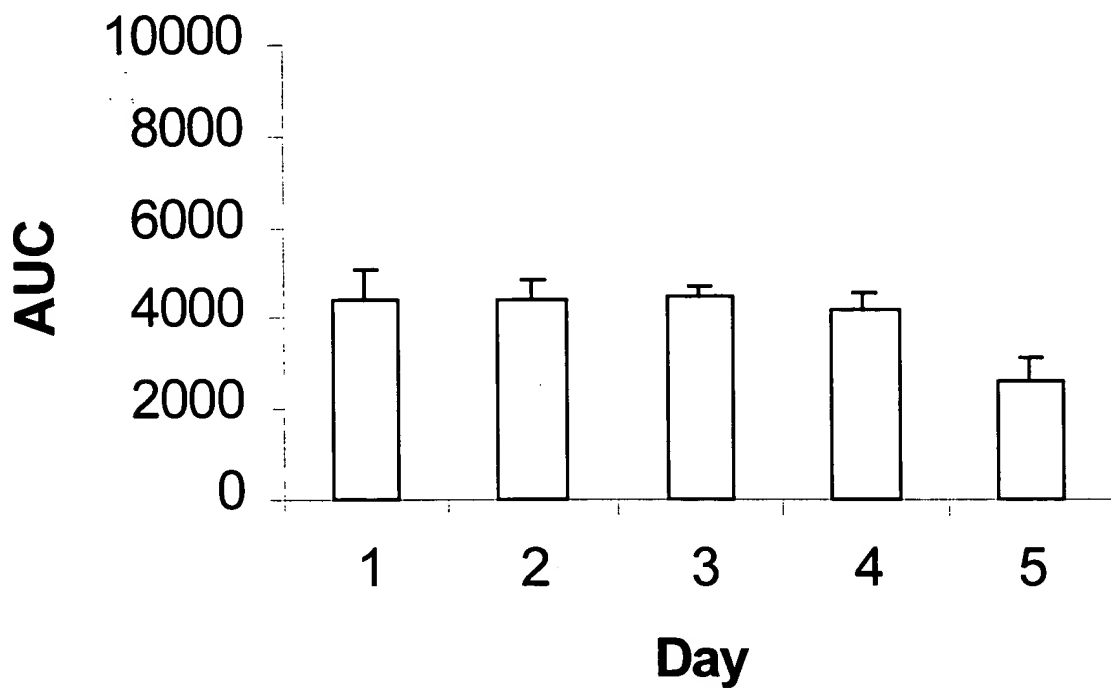


Figure 7

**0.2ug ESP7+2CD - 0.2ug naltrexone
(Days 2&4)**

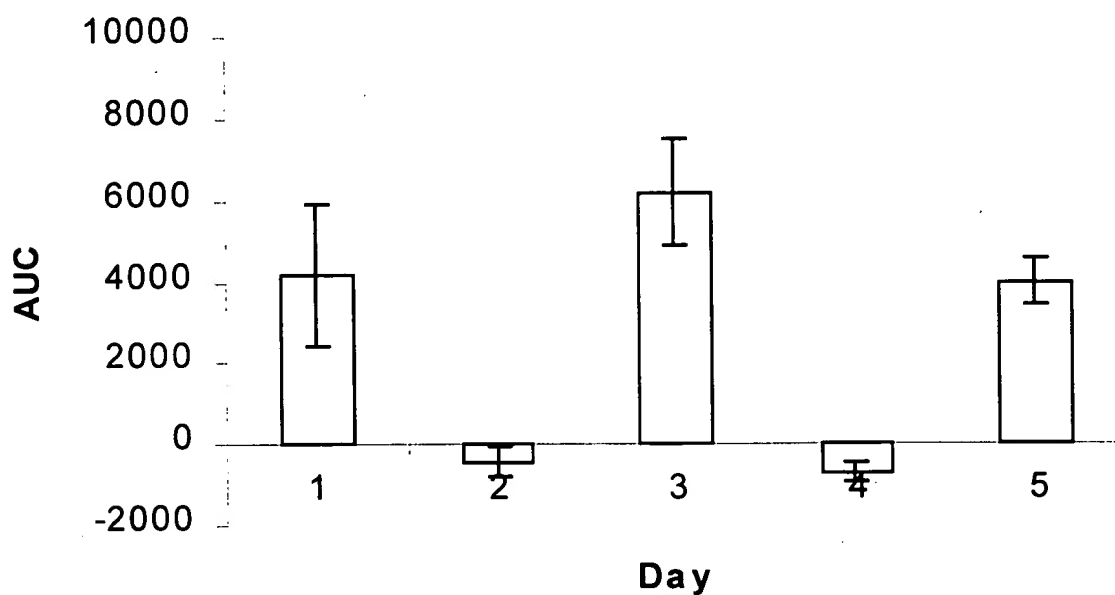


Figure 8

**1.0 ug ESP+2CD (Days1-5)- 250 pmol
RP67580 (Days 1-4) n=6**

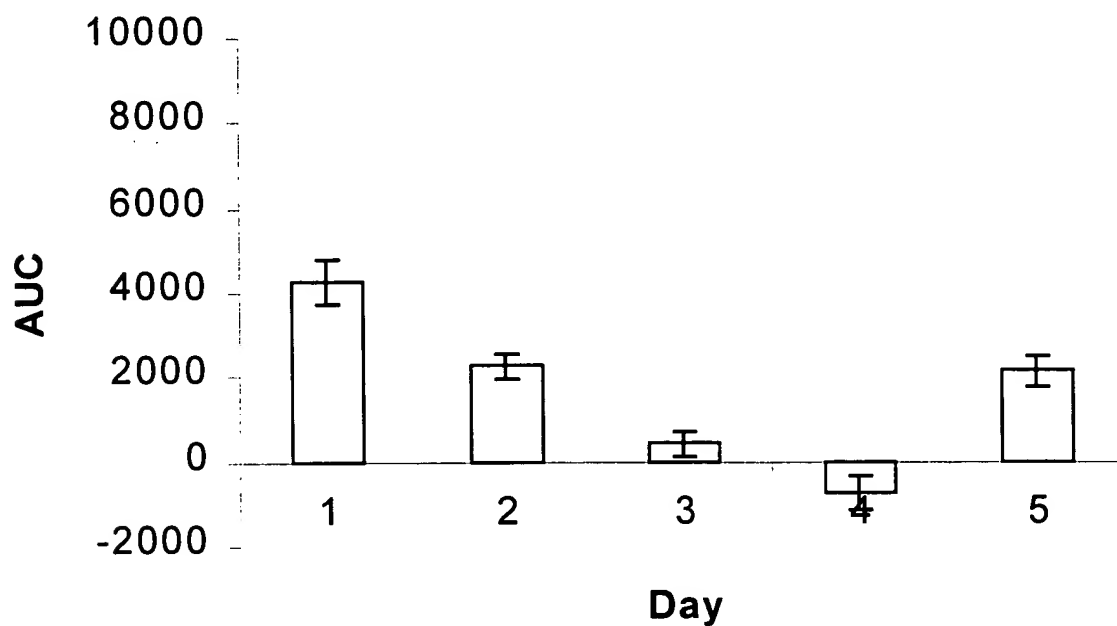


Figure 9

0.1 ug ESP7+2CD (i.c.v) n=4

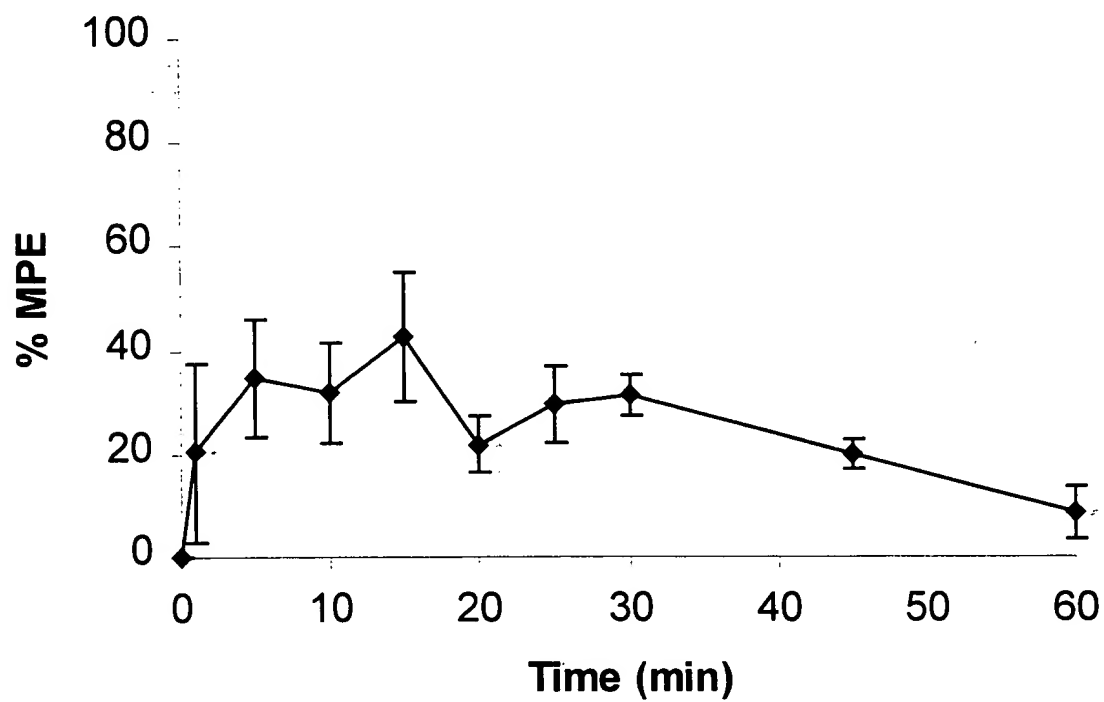


Figure 10

1 mg ESP7 (i.p.) n=7

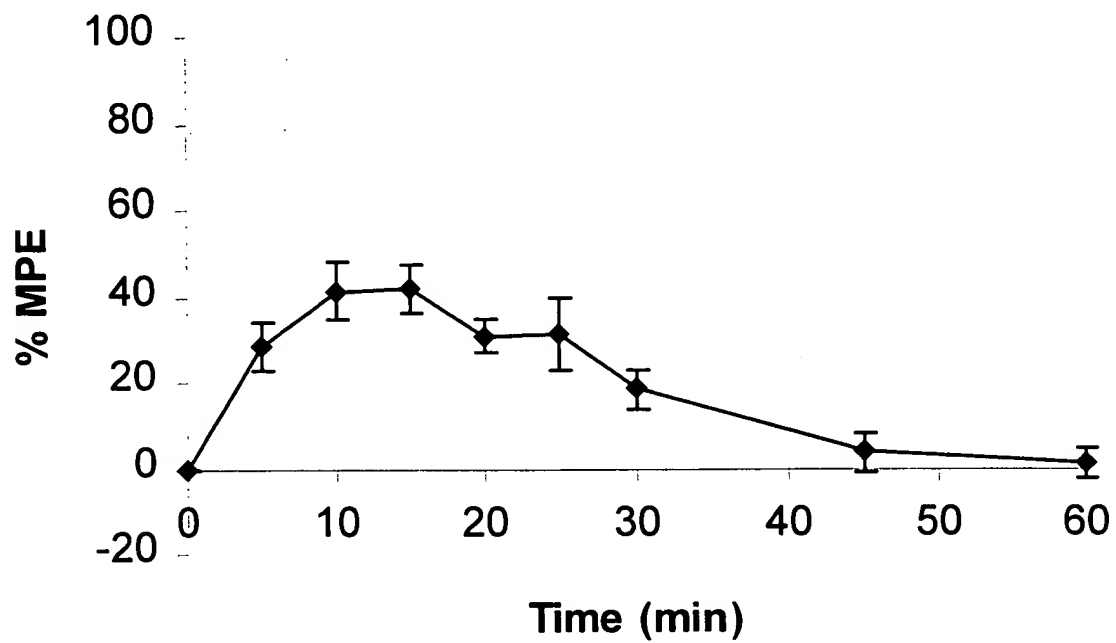


Figure 11